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## Description

The present invention relates to analgesic compositions comprising capsaicin or a capsaicin analog combined with a drug selected from the class of non-steroidal anti-inflammatory, antipyretic and analgesic compounds. These compositions, when administered to humans or lower animals, provide a synergistic analgesic effect while minimizing undesirable side effects and toxicity.

Capsaicin and its derivatives appear to produce an analgesic effect through a mechanism largely unrelated to that of the other two categories of analgesics opioids (narcotics) and non-steroidal analgesics (aspirin-like drugs). Since both capsaicin and the non-steroidals produce an analgesic effect, although apparently through different mechanisms, it might be expected that their combined effect would be at best additive. However, tests have shown that the analgesic effect of the combination is not merely the sum of the effects of each component, but rather an unexpected, greatly enhanced synergistic effect. Furthermore, the undesirable side effects of the two categories of analgesics are not closely related and the addition of the second analgesic does not appear to potentiate the side effects of the first. It is therefore possible to combine the two analgesics in such a dosage as to provide greatly enhanced analgesia with no enhancement of side effects. Depending on the dosages employed, the capsaicin may either potentiate the degree of analgesia beyond that obtainable using the non-steroidal alone, or it may induce analgesia at dosages where no analgesic effect is obtained from either component alone.

Traditionally, analgesics have fallen into two broad categories. Simple, non-narcotic analgesics, such as aspirin, which appear to work by inhibition of prostaglandin synthetase, are effective against pain of integumental origin such as headache and muscle aches, but are often ineffective in controlling deeper, more intense pain. Furthermore, they may cause undesirable side effects even at therapeutic dosages. The most common of these side effects is a propensity to induce dyspepsia and gastrointestinal bleeding. At higher dosages, the salicylates may have toxic effects on the central nervous system consisting of stimulation (including convulsions) followed by depression. Headache, diziness, mental confusion, hearing difficulties and hyperventilation may also occur. Gastrointestinal symptoms may include epigastric distress, nausea and vomiting. The narcotic analgesics appear to work through interaction with the endorphin/enkephalin receptor system of the central nervous system and are useful in controlling pain which is too intense to be controlled by the weaker, non-narcotic analgesics. However, centrally-acting narcotic analgesics have several serious undesirable side effects, including the development of physical dependence and tolerance, sedation, respiratory depression, hypotension, increase in cerebrospinal fluid pressure, nausea, vomiting and constipation. In some patients, particularly the chronically ill, the narcotic side effects make it impossible to administer dosages sufficient to adequately control pain over the required time period.

This invention combines capsaicin or a capsaicin analog with a drug from the class of non-narcotic, non-steroidal anti-inflammatory, antipyretic and analgesic compounds producing a synergistic increase in analgesia without a corresponding increase in side effects. The degree of analgesia produced by this combination has been found in some cases to be equivalent to that formerly obtainable only through the use of narcotics. Thus, the claimed combination makes it possible to control pain which is too severe to be adequately controlled by the non-steroidals alone, whle avoiding the serious side effects and addiction potential inherent in the use of opioids.

It has been recently discovered that capsaicin, a natural product of certain species of the genus *Capsicium*, induces analgesia. Capsaicin (8-methyl-N-vanillyl-6Z-nonenamide) and "synthetic" capsaicin (N-vanillyl-nonanamide) are disclosed as analgesics in US—A—4,313,958, LaHann, issued February 2, 1982. Analgesic activity of capsaicin has also been discussed in the chemical and medical literature, including Yaksh, et al, *Science, 206,* pp 481—483 (1979); Jancso, et al, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, Vol. 311, pp 285—288 and Holzer et al, *Eur. J. Pharm.* Vol. 58, pp 511—514 (1979). US—A—4,238,505, Nelson, issued December 9, 1980, discloses 3-hydroxyacetanilide for use in producing analgesia in animals. EP—A—0089710, La Hann, et al, published September 28, 1983, describes hydroxyphenylacetamides with analgesic and anti-irritant activity. Similarly, analgesic and anti-irritant activity is disclosed for N-vanillylsulfonamides in US—A—4,401,663, Buckwalter, et al, issued August 30, 1983; N-vanillylureas in EP—A—0068590, Buckwalter, et al, published January 5, 1983; N-vanillylcarbamates in EP—A—0068592, Buckwalter, et al, published January 5, 1983; N-[(substituted phenyl)methyl]alkynlamides in US—A—4532139; methylene substituted N-[(substituted phenyl)methyl-alkanamides in US—A—4544668, N[(substituted phenyl)methyl]-cis-monounsaturated alkenamides in US—A—4493848; and N-[substituted phenyl)methyl]-diunsaturated amides in US—A—4544669. However, non of these references suggest in any way the desirability of concurrent administration of capsaicin or a capsaicin derivative with a non-steroidal. Further, the art suggests that it is extremely difficult to predict when a synergistic effect will be obtained from the concurrent administration of two pharmaceutical compounds which take effect through different mechanisms.

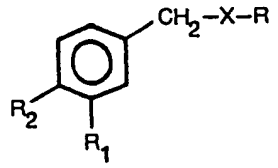
Although there are many patents which disclose analgesic and anti-inflammatory compositions containing a combination of two or more mechanistically unrelated analgesic and/or anti-inflammatory compounds, none of these compounds has a structure at all similar to that of capsaicin. See US—A—4,404,210, Schmidt, issued September 13, 1983; US—A—4,083,981, Yamamoto, issued April 11, 1978; US—A—4,315,936, Capetola et al, issued February 16, 1982; US—A—4,379,789, Capetola et al, issued

April 12, 1983; and US—A—4,275,059, Flora, et al, issued June 23, 1981.

Thus, based on the art, one could not have predicted that the combination of capsaicin or a capsaicin analog with a non-steroidal would result in a synergistic increase in analgesia.

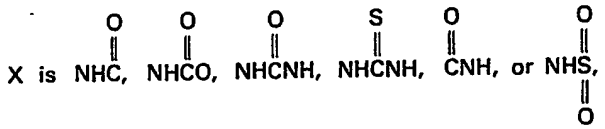
## SUMMARY OF THE INVENTION

It has now been found that combinations of capsaicin derivatives of the general formula



wherein $R_1$ is OH or $OCH_3$, $R_2$ is OH or

$R_3$ is $C_1$—$C_4$ alkyl or phenyl,



and R is a $C_{11}$—$C_{23}$ *cis* alkenyl, $C_{11}$—$C_{23}$ alkynyl, $C_{11}$—$C_{23}$ alkadienyl, or $C_{11}$—$C_{23}$methylene substituted alkane, with an arylalkanoic non-steroidal analgesic selected from ibuprofen, naproxen, ketoprofen, fenoprofen, suprofen, flurbiprofen, benoxoprofen, pirprofen and carprofen, at weight ratios of capsaicinoid to non-steroidal from 20:1 to 1:20, and preferably from 10:1 to 1:10, provide unexpectedly enhanced analgesic activity in humans and lower animals without a corresponding increase in undesirable side effects.

*Definitions*

By the term "comprising" as used herein is meant that various other inert ingredients, compatible drugs and medicaments, and steps can be employed in the compositions and methods of the present invention as long as the critical capsaicinoid/non-steroidal combination is present in the compositions and is used in the manner disclosed. The term "comprising" thus encompasses and includes the more restrictive terms "consisting essentially of" and "consisting of" which characterize the use of the composition and methods disclosed herein.

By "compatible" herein is meant that the components of the composition are capable of being commingled without interacting in a manner which would substantially decrease the analgesic efficacy of the total composition under ordinary use situations.

By "administer concurrently" is meant either the administration of a single composition containing both the capsaicinoid and the non-steroidal, or the administration of the capsaicinoid and the non-steroidal as separate compositions within a short enough time period that the effective result is equivalent to that obtained when both compounds are administered as a single composition. Normally this would involve two separate dosages given within 10 minutes of each other. However, since many capsaicinoids retain effectiveness over unusually long time periods (possibly up to 3 days in the same cases) and most non-steroidals provide effective analgesia for relatively short time periods (4—8 hours), it may be desirable in some cases to implement a therapeutic regimen whereby each component is administered according to a schedule determined by its own period of analgesic effectiveness in order to maintain optimum effectiveness of the combination. The preferred method of administration is as a single composition.

All percentages and ratios herein are by weight unless otherwise specified.

*Compositions*

The compositions of the present invention comprise a safe and effective amount of:

(a) a specified capsaicin analog,

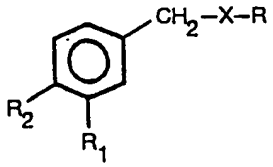
(b) a compound selected from specified non-steroidal analgesic drugs, and their pharmaceutically-acceptble salts; and

(c) a pharmaceutically-acceptable carrier.

A safe and effective amount of the composition is that amount which provides analgesia, thereby alleviating or preventing the pain being treated at a reasonable benefit/risk ratio, as is intended with any medical treatment. Obviously, the amount of the composition used will vary with such factors as the

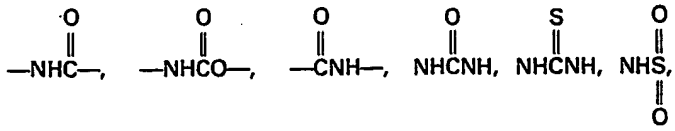
particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), the method of administration, and the specific formulation and carrier employed.

By the term "capsaicin analog" or "capsaicinoid" is meant a compound of the general formula



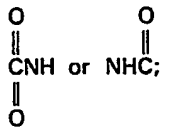
wherein $R_1$ is selected from OH and $OCH_3$, $R_2$ is selected from OH and

$R_3$ is selected from a $C_1$—$C_4$ alkyl and phenyl, X is selected from

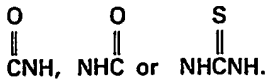


and R is selected from $C_{11}$—$C_{23}$ *cis* alkenyl, $C_{11}$—$C_{23}$ alkynyl, $C_{11}$—$C_{23}$ alkadienyl and $C_{11}$—$C_{23}$ methylene substituted alkane.

Preferred compounds include those wherein both $R_1$ and $R_2$ are OH and X is



and those wherein $R_1$ is $OCH_3$, $R_2$ is OH or $R_3CO$ and X is



Preferred R groups include $C_{16}$—$C_{21}$ *cis* alkenyls and alkadienyls. The preferred moieties within these groups include $C_{17}H_{33}$. Preferred capsaicin analogs include N-vanillyl-alkadienamides, N-vanillyl-alkanedienyls, and N-vanillyl-*cis*-monounsaturated alkenamides. A particularly preferred capsaicinoid is N-vanillyl-9E-octadecenamide (N-vanillyloleamide).

Preferred capsaicin analogs and methods for their preparation are described in the following Patents and Patent Applications; Capsaicin (8-methyl-N-vanillyl-6E-nonenamide) and "synthetic" capsaicin (N-vanillylnonanamide) are disclosed as analgesics in US—A—4,313,958, LaHann issued February 2, 1982. EP—A—0089710, La Hann, et al, published September 28, 1983, describes hydroxyphenylacetamides with analgesics and anti-irritant activity. Similarly, analgesic and anti-irritant activity is disclosed for N-vanillyl-sulfonamides in EP—A—0068591, Buckwalter, et al, published January 5, 1983; N-vanillylureas in EP—A—0068590, Buckwalter, et al, published January 5, 1983; N-vanillylcarbamates in EP—A—0068592, Buckwalter, et al, published January 5, 1983; N-[(substituted phenyl)methyl]alkynylamides in US—A—4,532,139; methylene substituted-N-[(substituted phenyl)methyl]-alkanamides in US—A—4,544,668; N[(substituted phenyl)methyl]-cis-monounsaturated alkenamides in US—A—4,493,848; and N-[(substituted phenyl)methyl]-diunsaturated amides in US—A—4,544,669.

Weight ratios of capsaicinoid to non-steroidal useful in the present invention range from 20:1 to 1:20, with the preferred ratio ranging from 10:1 to 1:10. The optimum weight ratio is dependent primarily upon the relative strength of the particular capsaicinoid and non-steroidal, used, and the type of severity of the pain being treated. As a representative example, preferred weight ratios of capsaicinoid:ibuprofen may range from 5:1 to 1:5.

By "pharmaceutically acceptable salts" is meant those salts of the above disclosed acids which are toxicologically safe for topical or oral administration. These include the sodium, calcium, potassium,

magnesium, ammonium, lysine, and arginine salts.

By "pharmaceutically acceptable carrier" is meant a solid or liquid filler, diluent or encapsulating substance which may be safely used in systemic or topical administration. Depending upon the particular route of administration, a variety of pharmaceutically-acceptable carriers, well-known in the art, may be used. These include solid or liquid fillers, diluents, hydroptropes, surface-active agents, and encapsulating substances. The amount of the carrier employed in conjunction with the capsaiconoid/opioid combination is sufficient to provide a practical quantity of material per unit dose of analgesic.

Pharmaceutically-acceptable carriers for systemic administration, that may be incorporated into the compositions of this invention, include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Specific pharmaceutically-acceptable carriers are described in US—A—4,401,663, Buckwalter, et al, issued August 30, 1983; EP—A—0089710, LaHann, et al, published September 28, 1983; and EP—A—0068592, Buckwalter, et al, published January 5, 1983. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, aqueous ethanol, sesame oil, corn oil, and combinations thereof.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring, and flavoring agents. Preferred carriers for oral administration include ethyl oleate, methyl cellulose, gelatin, propylene glycol, cottonseed oil, sesame oil, peanut oil, corn oil, soybean oil, oil and water emulsions, and self-emulsifying oils either as free-flowing liquids or encapsulated in soft gelatin capsules. Specific examples of pharmaceutically-acceptable carriers and excipients that may be used to formulate oral dosage forms, which may be used in formulating oral dosage forms containing monoalkenamides, are described in US—A—3,903,297. Robert, issued September 2, 1975. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms", *Modern Pharmaceutics, Vol. 7*, (Banker and Rhodes, editors), 359—427 (1979).

Specific systemic and topical formulations useful in this invention are described in the following Patents or Patent Applications, relating to specifc capsaicin analogs and methods of treatment; US—A—4,401,663, Buckwalter, et al, issued August 30, 1983; EP—A—0089710; La Hann, et al, published September 28, 1983; EP—A—0068590, Buckwalter, et al, published January 5, 1983; and EP—A—0068592, Buckwalter, et al, published January 5, 1983. Topical vehicles, useful herein, are disclosed in the following: "Improved Penetrating Topical Pharmaceutical Compositions Combining 1-dodecylazacycloheptan-2-one", US—A—4,557,934; "Penetrating Topical Pharmaceutical Compositions Containing N-(1-hydroxyethyl)-pyrrolidone", US—A—4,537,776; and "Compounds Useful for Producing Analgesia", US—A—4,493,848.

Dosages required, as well as methods of administration, are dependent on the type of non-steroidal employed, the physical condition of the patient, the severity of the pain which must be prevented or alleviated, the relative severity and importance of adverse side effects, and other factors within the judgment of the physician. The preferred method of administration in most cases will be orally.

The maximum dosage of the preferred capsaicin analogue vanillyloleamide (VO) which would normally be administered orally to an average adult without unacceptable side effects is about 2000 mg (35.4 mg/kg). The minimum effective dosage is about 50 mg (0.85 mg/kg). The maximum dosage of a non-steroidal which can be administered to the average adult is also about 2000 mg (35.4 mg/kg). Thus, the maximum allowable dosage of the combination will be about 2000 mg (35.4 mg/kg). It should be noted that a sub-effective dosage of one compound may effectively potentiate the other compound; therefore, less-than-minimum dosages of each component may be utilized in some cases. Thus, when dealing with safe and effective dosage levels of the present invention, it is more appropriate to speak of safe and effective dosages of the combination rather than of the individual components.

The compositions and combinations of this invention can be used to treat and prevent pain and inflammation associated with certain diseases, particularly muscular-skeletal disorders, and to provide analgesia in various disorders at the deeper structures, muscles, tendons, bursa and joints associated with disease and trauma, and in various other conditions in which capsaicinoids and/or non-steroidals have heretofore been used to alleviate pain and discomfort.

The compositions of the instant invention are normally administered either topically or orally.

The following non-limiting Examples illustrate the compositions of the present invention.

Example I

An analgesic composition for oral administration was made using the following ingredients:

| | |
|---|---|
| N-vanillyl-9E-octadecenamide | 120 mg |
| Ibuprofen | 30 mg |
| Methylcellulose | 30 mg |
| Saline | 6.0 ml |

The methylcellulose suspending agent was dissolved in the saline to yield a 0.5% solution, to which the two drugs were added. A homogeneous suspension was achieved by the aid of sonication. Male mice weighing approximately 25 g were dosed by gavage with 250 mg/kg of the mixture. Analgesic activity was demonstrated using the phenylquinone writhing test mixture. Angesic activity was demonstrated using the phenylquinone writhing test.

Example II

An analgesic composition for oral administration was made using the following ingredients:

| | |
|---|---|
| N-vanillyl-9E-octadecenamide | 120 mg |
| Ibuprofen | 30 mg |
| Ethyl oleate | 6.0 ml |

The two analgesic agents wree suspended in the ethyl oleate with the aid of sonication, and analgesic activity was demonstrated using the phenylquinone writhing test.

Example III

A composition for oral administration is made with the following components:

| | Bulk | Individual Tablet |
|---|---|---|
| N-vanillyl-9,12-octadecadienamide | 140 g | 350 mg |
| Ibuprofen | 35 g | 90 mg |
| Starch | 12 g | 30 mg |
| Magnesium stearate | 2 g | 5 mg |
| Microcrystalline cellulose | 40 g | 100 mg |
| Colloidal silicon dioxide | 1 g | 2.5 mg |
| Povidone | 5 g | 12.5 mg |

The above ingredients are admixed in bulk and formed into compressed tablets, using tabletting methods known in the art, each containing 590 mg of the mixture. One such tablet is administered orally to a 60 kg human, producing analgesia.

Example IV

A composition for transdermal topical delivery is made by admixing the following components:

| | |
|---|---|
| N-vanillyl-9,12,15[E,E,E]-octadecatrienamide | 4.0% |
| Ibuprofen | 1.0% |
| Myristyl alcohol | 1.0% |
| Propylene glycol | 94.0% |

Approximately 4.0 ml of the lotion is applied to an 80 sq cm portion of the skin of a 60 kg human, producing analgesia.

Effectiveness in Providing Analgesia Phenylquinone Writhing Tests

The extent of analgesia obtained was determined using the phenylquinone writhing test model. Groups of eight male mice weighing between approximately 25 and 30 g were dosed orally by gavage with the analgesic composition to be tested. Identical groups of mice were dosed with control compositions. Three hours after this initial administration, the mice were injected intraperitoneally with a 0.2% solution of phenylbenzoquinone in aqueous ethanol. The ability of the analgesic compositions tested to relieve the discomfort induced was measured by counting the number of abdominal contractions, or "writhes", occurring in each mouse during a 10 minute period beginning 10 minutes after injection of the phenylbenzoquinone solution. The results are expressed as a percent of the "writhing" response observed in the vehicle control group.

Example V

An analgesic composition for oral administration was made using the following ingredients:

| | |
|---|---|
| N-vanillyl-9-octadecenamide | 120 mg |
| Ibuprofen | 30 mg |
| Methylcellulose | 30 mg |
| Saline | 6.0 ml |

The methylcellulose suspending agent was dissolved in the saline to yield a 0.5% solution, to which the two drugs were added. A homogeneous suspension was achieved by the aid of sonication. The analgesic efficacy of this formulation was evaluated by dosing the mice by gavage with a sufficient dosage to provide 250 mg/kg of the mixture. The analgesic strength of the treatment was assessed using the "writhing" method described above. The efficacy of the combination was compared with that of similar formulations lacking the octadecenamide, the ibuprofen, or both.

| Treatment | % Writhing Response |
|---|---|
| Methylcellulose alone | 100 |
| Ibuprofen (50 mg/kg) | 114 |
| Octadecenamide (200 mg/kg) | 48 |
| Octadecenamide (200 mg/kg) + ibuprofen (50 mg/kg) | 2 |

In this case, the addition of an ineffective dose of ibuprofen to a moderately effective dose of octadecenamide resulted in a greatly potentiated analgesic effect.

Example VI

An analgesic composition for oral administration was made using the following ingredients:

| | |
|---|---|
| N-vanillyl-9-octadecenamide | 120 mg |
| Ibuprofen | 30 mg |
| Ethyl oleate | 6.0 ml |

The two analgesics were suspended in ethyl oleate with the aid of sonication, and evaluated for analgesic efficacy exactly as described in Example X.

| Treatment | % Writhing Response |
|---|---|
| Ethyl oleate alone | 100 |
| Octadecenamide (200 mg/kg) | 36 |
| Ibuprofen (50 mg/kg) | 154 |
| Octadecenamide (200 mg/kg) + ibuprofen (50 mg/kg) | 5 |

Although the response of the group receiving 50 mg/kg of ibuprofen alone did not vary significantly from that of the control group, the addition of this sub-effective amount of ibuprofen to the octadecenamide greatly potentiated its analgesic effect. Further, the combination of ibuprofen with the octadecanamide can provide anti-inflammatory/anti-arthritis efficacy lacking in N-vanillyl-9-octadecenamide and related capsaicin analogs.

Example VII

In order to determine the preferred dosages of the capsaicinoid/non-steroidal combination in the rat, a 2:1 octadecenamide:ibuprofen analgesic composition for oral administration was made using the following ingredients:

| | |
|---|---|
| N-vanillyl-9E-octadecenamide | 100 mg |
| Ibuprofen | 50 mg |
| Ethyl oleate/benzyl alcohol (98:2 vol/vol) | 5 ml |

The two analgesics were suspended in the ethyl oleate solution with the aid of sonication, and varying dosages of the combination, as well as the individual components, were evaluated for analgesic efficacy as dscribed in Example X.

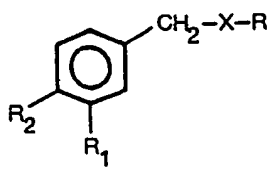
| Treatment | % Writhing Response |
|---|---|
| Ethyl oleate solution alone | 100 |
| 50 mg/kg ibuprofen | 150 |
| 100 mg/kg octadecenamide | 83 |
| 400 mg/kg octadecenamide | 21 |
| 75 mg/kg 2:1 octadecenamide: ibuprofen combination | 40 |
| 150 mg/kg 2:1 octadecenamide: | 6 |
| 300 mg/kg 2:1 octadecenamide: ibuprofen combination | 0.5 |

All three dosage levels of the combination produced a significant analgesic effect, although the 75 mg/kg dosage produced less analgesia than the other two dosages. Preferred dosage levels will depend on the severity of the pain to be treated, the relative severity of adverse side effects, and other factors within the judgment of the physician.

Although neither 50 mg/kg ibuprofen nor 100 mg/kg octadecenamide provided significant analgesia by themselves, the 150 mg/kg combination (100 mg/kg octadecenamide + 50 mg/kg ibuprofen) demonstrated an extremely strong analgesic effect. Furthermore, only 150 mg/kg of the 2:1 combination produced a greater analgesic effect than 400 mg/kg of octadecenamide alone, and only 75 mg/kg of the 2:1 combination (sub-effective amounts of both components) produced a greater analgesic effect than 100 mg/kg of octadecenamide alone. These results indicate a synergistic increase in analgesia when the two analgesics are combined.

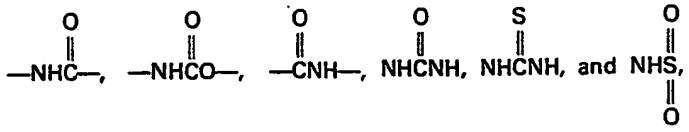
**Claims**

1. An analgesic composition characterised in that it comprises a safe and effective amount of:
a) an analgesic compound of the general formula




wherein $R_1$ is selected from OH and $OCH_3$, $R_2$ is selected from OH and

$R_3$ is selected from $C_1$—$C_4$ alkyl and phenyl, X is selected from

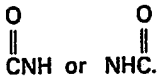


and R is selected from $C_{11}$—$C_{23}$ *cis* alkenyl, $C_{11}$—$C_{23}$ alkynyl, $C_{11}$—$C_{23}$ alkadienyl and $C_{11}$—$C_{23}$ methylene substituted alkane;

b) an arylalkanoic non-steroidal analgesic selected from ibuprofen, naproxen, ketoprofen, fenoprofen, suprofen, flurbiprofen, benzoxaprofen, pirprofen and carprofen; and

c) a pharmaceutically-acceptable carrier; wherein the weight ratio of (a):(b) is from 20:1 to 1:20.

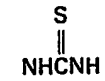
2. A composition according to Claim 1, characterized in that $R_1$ and $R_2$ are both OH and X is



3. A composition according to Claim 1, characterized in that $R_1$ is $OCH_3$, $R_2$ is OH, and X is

4. A composition according to Claim 3, characterized in that R is a $C_{16}$—$C_{21}$ *cis* alkenyl or $C_{16}$—$C_{21}$ alkadienyl.

5. A composition according to Claim 1, characterized in that $R_1$ is $OCH_3$, $R_2$ is OH, X is



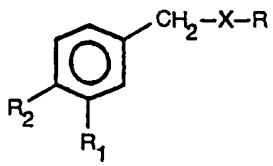
and R is $C_{16}$—$C_{21}$ alkadienyl.

6. A composition according to Claim 1, characterized in that the capsaicinoid is N-vanillyl-9-octadecenamide.

**Patentansprüche**

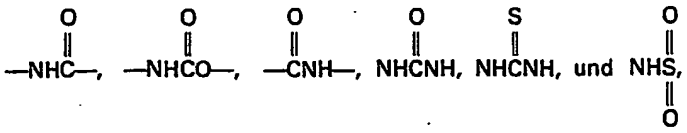
1. Eine analgesische Zusammensetzung, dadurch gekennzeichnet, dass sie eine sichere und wirksame Menge

a) einer analgesischen Verbindung der allgemeinen Formel



worin $R_1$ ausgewählt ist aus OH und $OCH_3$, $R_2$ ausgewählt ist aus OH und

$R_3$ ausgewählt ist aus $C_1$—$C_4$-Alkyl und Phenyl, X ausgewählt ist aus



und R ausgewählt ist aus einem $C_{11}$—$C_{23}$-cis-Alkenyl-, $C_{11}$—$C_{23}$-Alkynyl-, $C_{11}$—$C_{23}$-Alkadienyl und einem $C_{11}$—$C_{23}$-Methylen-substituierten Alkanrest,

b) einer nicht-steroiden, analgesischen Arylalkansäureverbindung, ausgewählt aus Ibuprofen, Naproxen, Ketoprofen, Fenoprofen, Suprofen, Flurbiprofen, Benoxaprofen, Pirprofen und Carprofen, und

c) einen pharmazeutisch zulässigen Träger enthält, worin das Gewichtsverhältnis von (a) zu (b) 20:1 bis 1:20 beträgt.

2. Eine Zusammensetzung gemäss Anspruch 1, dadurch gekennzeichnet, dass $R_1$ und $R_2$ beide OH und X

sind.

3. Eine Zusammensetzung gemäss Anspruch 1, dadurch gekennzeichnet, dass $R_1$ $OCH_3$, $R_2$ OH und X

ist.

4. Eine Zusammensetzung gemäss Anspruch 3, dadurch gekennzeichnet, dass R einen $C_{16}$—$C_{21}$-cis-Alkenyl oder einen $C_{16}$—$C_{21}$-Alkadienylrest bedeutet.

5. Eine Zusammensetzung gemäss Anspruch 1, dadurch gekennzeichnet, dass $R_1$ $OCH_3$, $R_2$ OH, X

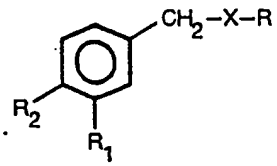
und R ein $C_{16}$—$C_{21}$-Alkadienylrest ist.

6. Eine Zusammensetzung gemäss Anspruch 1, dadurch gekennzeichnet, dass das Capsaicinoid N-Vanillyl-9-octadecenamid ist.

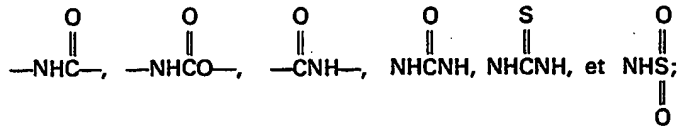
**Revendications**

1. Composition analgésique, caractérisée en ce qu'elle comprend une quantité sans danger et efficace:

a) d'un composé analgésique de formule générale



dans laquelle $R_1$ est choisi parmi OH et $OCH_3$, $R_2$ est choisi parmi OH ou $OCR_3$, $R_3$ est choisi parmi un groupe alkyle en $C_1$—$C_4$ et un groupe phényle, X est choisi parmi



et R est choisi parmi un groupe cis-alcényle en $C_{11}$—$C_{23}$, alcynyle en $C_{11}$—$C_{23}$, alcadiényle en $C_{11}$—$C_{23}$ et un alcane substitué par un méthylène en $C_{11}$—$C_{23}$;

b) d'un analgésique arylalcanoïque non stéroïdien choisi parmi l'ibuprofen, le naproxen, le kétoprofen, le fénoprofen, le suprofen, le flurbiprofen, le bénoxoprofen, le pirprofen et le carprofen; et

c) d'un véicule pharmaceutiquement acceptable; le rapport pondéral de (a) à (b) étant de 20:1 à 1:20.

2. Composition selon la revendication 1, caractérisée en ce que $R_1$ et $R_2$ sont tous deux OH et X est

3. Composition selon la revendication 1, caractérisée en ce que $R_1$ est $OCH_3$, $R_2$ est OH et X est

4. Composition selon la revendication 3, caractérisée en ce que R est un groupe cis-alcényle en $C_{16}$—$C_{21}$ ou alcadiényle en $C_{16}$—$C_{21}$.

5. Composition selon la revendication 1, caractérisée en ce que $R_1$ est $OCH_3$, $R_2$ est OH, X est

et R est un groupe alcadiényle en $C_{16}$—$C_{21}$.

6. Composition selon la revendication 1, caractérisée en ce que le capsaïcinoïde est le N-vanillyl-9-octadécénamide.